Microscopic Modelling of the Non-Linear Gap Junction Channels

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On Gap Junctions

- **What is a Gap Junction?**
  - Cluster of gap junction channels
  - Linking structure between neighbouring cells
  - Provides direct passage of molecules and ions

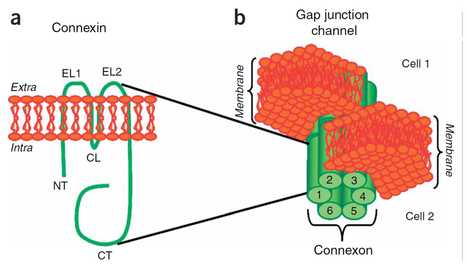


Figure : Schematic diagrams of a standard connexin molecule and gap junction channel. (Del Corso et. al., 2006)

- **What are they made of?**
  - Proteins connexins.
  - 6 connexins = 1 connexon (hemichannel)
  - 2 connexons = 1 gap junction channel
  - Cardiac cell proteins: Cx43, Cx45 and Cx40.

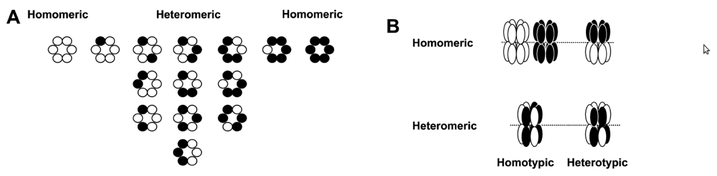


Figure : Predicted configurations of connexons and gap junction channels for two different connexins. (Desplantez, 2004)

- **Where are they located in cardiac cells?**
  - Mostly on the longitudinal ends where they compose the intercalated disks
  - The behaviour of transversal GJ channels is not well understood

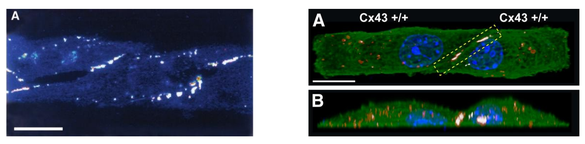
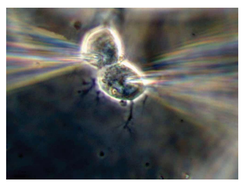


Figure : Immunohistochemical analysis of Cx43. Left: Bar = $10\mu m$. (Beauchamp, 2004) Right: top view(A), lateral view(B). Bar = $5\mu m$. (Beauchamp, 2012)

- **What about electrical behaviour?**
  - The dual voltage patch clamp
  - **Non-linear behaviour**
  - **Time dependence**
  - Dependent on connexin arrangement.



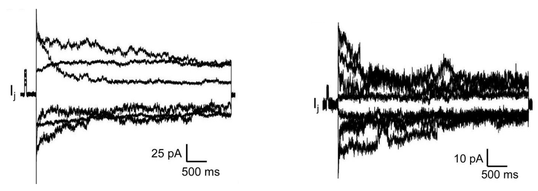
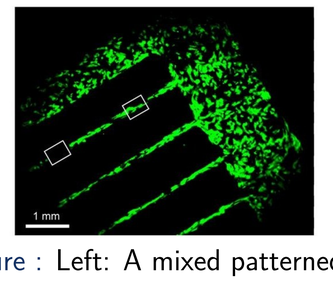


Figure : GJ currents in time, fixed V_j. Left: Homotypic Cx43/Cx43 cell pairs. Right: Cx43KO/Cx43KO cell pairs.

Macroscopic effects

- Primary cultures of Cx43 and Cx43KO ventricular myocytes.
- Macroscopic velocity calculated from the difference in activation times



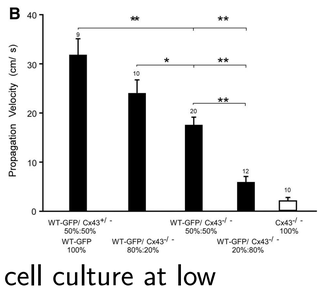


Figure : Left: A mixed patterned cell culture at low magnification. Right: Decrease in velocity of propagation w.r.t. presence of Cx43 cells.

Non linear GJ model - 0D

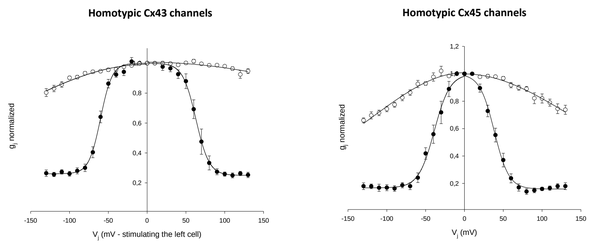
- GJ current:

$$I_j = G_j(t, V_j)V_j,$$

where:
  - V_j transjunctional voltage.
  - Conductance: $G_j(t, V_j) = g_{j,0}g_j(t, V_j)$.
  - The amplitude of the junctional conductance: $g_{j,0} = 68nS$ for Cx43 cells, i.e. $g_{j,0} = 2nS$ for Cx43KO.
  - Gating variable: $g_j = g_j(t, V_j)$

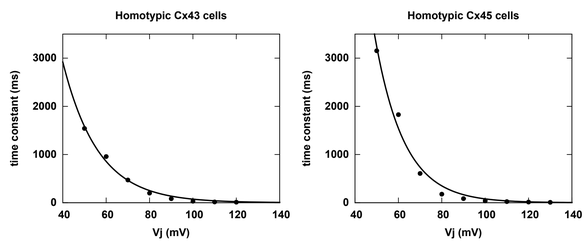
$$\frac{dg_j}{dt} = \frac{g_\infty(V_j) - g_j}{\tau_\infty(V_j)}$$

- Fit experimental data to find normalised $g_\infty(V_j)$.



Dual voltage clamp recordings performed in stably transfected (single transfection) HeLa cells

- Fit experimental data to find $\tau_\infty(V_j)$.



Numerical simulation

- Assume uniform distribution of GJ channels over given area (see 2D model)

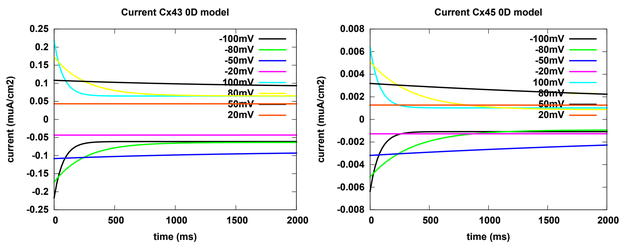
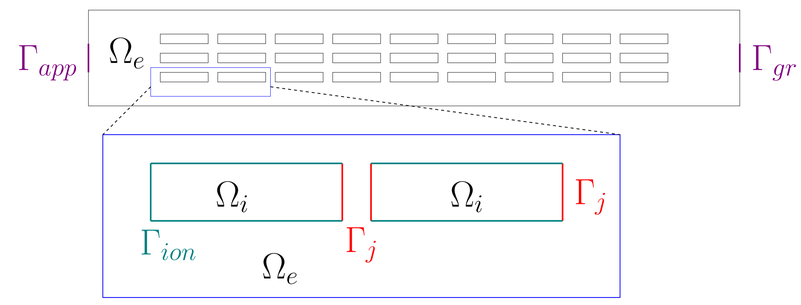


Figure : Simulated GJ current per unit area w.r.t. the time for the fixed V_j.

Assumptions

- Use only homotypic Cx43 and Cx45 GJ channels.
- GJ channels are at the perimeters of the cells, on the membrane.
- The rest of the membrane has only ionic channels. Use Beeler Reuter ionic model.

2D microscopic model



Main problem:

$$\begin{aligned} \sigma^i \Delta u_i &= 0, && \text{in } \Omega_i, \\ \sigma^e \Delta u_e &= 0, && \text{in } \Omega_e. \end{aligned}$$

Ionic model:

$$\left.\begin{aligned} \partial_t V_m + I_{ion}(V_m, \mathbf{h}) &= -\sigma_i \nabla u_i \cdot \mathbf{n}, \\ \partial_t V_m + I_{ion}(V_m, \mathbf{h}) &= -\sigma_e \nabla u_e \cdot \mathbf{n}, \\ \partial_t \mathbf{h} &= f_{ion}(V_j, \mathbf{h}), \end{aligned}\right\} \quad \text{on } \Gamma_{ion}.$$

GJ model:

$$\left.\begin{aligned} G_j(V_j, g_j) \cdot V_j &= -\sigma_i \nabla u_i \cdot \mathbf{n}, \\ \partial_t g_j &= f_j(V_m, g_j), \end{aligned}\right\} \quad \text{on } \Gamma_j.$$

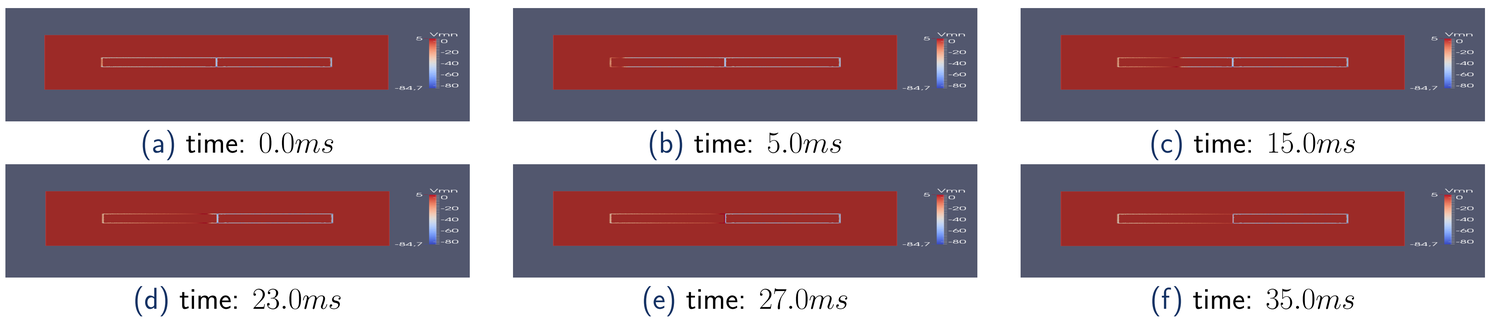
Boundary conditions and stimulus:

$$\begin{aligned} \sigma_e \nabla u_e \cdot \mathbf{n} &= 0, && \text{on } \partial\Omega_e \setminus \Gamma_{ion}, \\ u_e &= 0, && \text{on } \Gamma_{gr}, \\ \text{for } t \in [t_0, t_0 + t_{stim}], & \\ u_e &= U_{app}, && \text{on } \Gamma_{app}. \end{aligned}$$

- σ_i, σ_e intra and extracellular conductivities
- $\mathbf{h}$ gating variables for ionic model
- $V_m = u_i - u_e$ transmembrane potential
- $V_j = [u_i]$ transjunctional potential

Numerical analysis - 2D test case

- Domain: 2×1 cells, cell size $100 \times 20\mu m$, distance $1\mu m$. Mesh and time step: $dx = 1\mu m$, $dt = 0.02ms$.
- BR ionic model. Semi-implicit time scheme. FEM. Iterative method. Test: **no gap junctions**.



(a) time: $0.0ms$ (b) time: $5.0ms$ (c) time: $15.0ms$

(d) time: $23.0ms$ (e) time: $27.0ms$ (f) time: $35.0ms$

On going work

- Current observations: without GJ there is no AP propagation from cell to cell.
- To be tested: finer mesh, smaller cell distances.
- Include different types of GJCs on larger domains.
- Compare velocities with the experimental observations.

Future work:

- Move to homogenised model.

References

[1] Beauchamp et al. Circulation research 95.2 (2004): 170-178.

[2] Beauchamp et al. Circulation research 110.11 (2012): 1445-1453.

[3] del Corsso et al, Nature protocols 1.4 (2006): 1799-1809.

[4] Desplantez et al. Pflugers Arch. 2004 Jul;448(4):363-75

[5] Desplantez et al. J Membr Biol. 2007 Aug;218(1-3):13-28

[6] L Harris. Quarterly reviews of biophysics 34.03 (2001): 325-472.

[7] Hand and Peskin. Bulletin of mathematical biology 72.6 (2010): 1408-1424.